PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC26077A	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/IB2005/000263	International filing date *(day/month/year)* 05.01.2005	Priority date *(day/month/year)* 13.01.2004
International Patent Classification (IPC) or national classification and IPC INV. C07D487/04 A61K31/5517 A61P25/00		
Applicant PFIZER LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.02.2005	20.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer De Jong, B Telephone No. +31 70 340-2833

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2005/000263

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-45 as originally filed

   Claims, Numbers

   1-14 received on 17.06.2005 with letter of 17.06.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 6-9 (with respect to industrial application)

because:

☒ the said international application, or the said claims Nos. 6-9 (with respect to industrial application) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-5,10-14
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III.

Claims 6-9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

Reference is made to the following documents:

D1 : WO 01/58880 A (TOBE TAKAHIKO) 16 August 2001

Document D1, which is considered to represent the most relevant state of the art, discloses triazolo derivatives of formula (I) as V1a receptor antagonists. In view of this prior art the problem was to provide alternative V1a receptor antagonists. It is credible that this problem has been solved by the provision of the tetraaza-benzo[e]azulene compounds. Since these compounds are not obvious from D1, the compounds of claims 1-5 and their use (claims 6-14) are considered as inventive.

For the assessment of the present claims 6-9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims.

Re Item VIII.

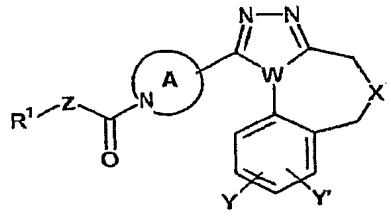
The application does not meet the requirements of Article 6 PCT, because claim 1 is not clear:

The term "acceptable derivative" obscures the meaning of claim 1. Furthermore, on page 7 it is said that the scope of the inventon also includes "prodrugs". This makes the scope of claim 1 unclear.

PC26077

CLAIMS:

1. A compound of formula **(I)**,



(I)

or a pharmaceutically acceptable derivative thereof, wherein:

X represents NR or O;

R represents hydrogen, C_{1-8} alkyl or $SO_2[C_{1-8}$ alkyl];

W represents N;

Y and Y' independently represent hydrogen, halogen, OH, CF_3, OCF_3, CN, NH_2, C_{1-8} alkyl, C_{1-8} alkyloxy or C_{3-8} cycloalkyl;

Ring **A** represents a heterocyclic ring containing at least one nitrogen atom;

Z represents a direct link, C_{1-8} alkyl or C_{3-8} cycloalkyl;

R^1 represents R^2, OR^2, OR^3-R^4, $N(R^2)[C_{1-8}$ alkylene$]_aR^4$; $NCOR^2$, or SR^4;

R^2 and R^4 independently represent hydrogen, C_{3-8} cycloalkyl, CF_3, Ar or Het;

R^3 represents a direct link or C_{1-8} alkyl;

a is 0 or 1;

Ar represents an aromatic ring, optionally fused to a heterocyclic ring, and/or optionally substituted with one or more groups as described below;

Het represents a heterocyclic ring optionally substituted with one or more groups as described below, and/or optionally fused to an aromatic ring which is optionally substituted with one or more groups as described below;

at each occurrence C_{1-8}alkyl, C_{1-8}alkylene and C_{3-8}cycloalkyl may be independently optionally substituted with one or more groups as described below;

substituent groups for Ar, Het, C_{1-8}alkyl, C_{1-8}alkylene and C_{3-8}cycloalkyl referred to above are independently selected from hydrogen, halogen, C_{1-8}alkyl, C_{1-8}alkyloxy, $S[C_{1-8}$alkyl], CN, CF_3, NH_2 and OH.

2. A compound according to claim 1, wherein X represents NR and R represents Me.

3. A compound according to claims 1 or 2, wherein Ring **A** represents piperidinyl.

4. A compound according to any of claims 1 to 3, wherein Z is a direct link.

5. A compound according to claim 1, selected from

[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-piperidin-1-yl]-(1H-indol-3-yl)-methanone;

1-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e] azulen-1-yl)-piperidin-1-yl]-2-o-tolyl-ethanone;

[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-piperidin-1-yl]-(1-methyl-cyclohexyl)-methanone;

1-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e] azulen-1-yl)-piperidin-1-yl]-2-cyclopropyl-ethanone;

[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-piperidin-1-yl]-(1H-indol-2-yl)-methanone;

[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-piperidin-1-yl]-(2-hydroxy-5-methyl-phenyl)-methanone;

[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-piperidin-1-yl]-(1H-indol-6-yl)-methanone;

[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-piperidin-1-yl]-(3-methoxy-phenyl)-methanone ;

[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-piperidin-1-yl]-(3-fluoro-phenyl)-methanone;

[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-piperidin-1-yl]-(4-fluoro-phenyl)-methanone;

1-[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-piperidin-1-yl]-butan-1-one;

[4-(8-Chloro-5-methyl-5,6-dihydro-4H-2,3,5,10b-tetraaza-benzo[e]azulen-1-yl)-piperidin-1-yl]-cyclopropyl-methanone; and

pharmaceutically acceptable derivatives thereof.

6. The use of a compound according to any of claims 1 to 5 as a medicament.

7. A method of treatment of anxiety, cardiovascular disease (including angina, atherosclerosis, hypertension, heart failure, edema, hypematremia), dysmenorrhoea (primary and secondary), endometriosis, emesis (including motion sickness), intrauterine

growth retardation, inflammation (including rheumatoid arthritis), mittelschmerz, preclampsia, premature ejaculation, premature (preterm) labor or Raynaud's disease, comprising administering a therapeutically effective amount of a compound according to any of claims 1 to 5 to a patient suffering from such a disorder.

8. A method according to claim 6 wherein the disorder is dysmenorrhoea (primary or secondary).

9. A method according to claim 8 wherein the disorder is primary dysmenorrhoea.

10. The use of a compound according to any of claims 1 to 5 in the manufacture of a medicament for the treatment of anxiety, cardiovascular disease (including angina, atherosclerosis, hypertension, heart failure, edema, hypernatremia), dysmenorrhoea (primary and secondary), endometriosis, emesis (including motion sickness), intrauterine growth retardation, inflammation (including rheumatoid arthritis), mittelschmerz, preclampsia, premature ejaculation, premature (preterm) labor or Raynaud's disease.

11. Use according to claim 10 wherein the disorder is dysmenorrhoea (primary or secondary).

12. Use according to claim 11 wherein the disorder is primary dysmenorrhoea.

13. A pharmaceutical formulation including a compound according to any of claims 1 to 5 or a pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable excipients, diluent or carrier;

14. A pharmaceutical product containing a V1a antagonist according to any of claims 1 to 5 in combination with a compound selected from (a) an oral contraceptive, (b) a PDE5 inhibitor, (c) an NO donor, (d) L-arginine, or (e) a COX inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of dysmenorrhoea.